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Zonisamide overview of the United States experience

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Although established antiepilepsy drugs (AEDs) are efficacious and new drugs have become available to treat patients with epilepsy, at least 30% of all patients remain refractory to available treatment.[1] Continued efforts to identify and develop new compounds for the treatment of epilepsy motivate all concerned because of the plight of so many patients. In the following sections, data are provided that document the US experience in the development and ultimate availability of zonisamide for treatment of patients with partial seizures.

Development of zonisamide in the United States began in 1982 as a collaborative project between Dainippon Pharmaceuticals Co, and Parke-Davis. Pilot studies of bioavailability and pharmacokinetics involved about 270 healthy volunteers and also patients with epilepsy. Both open and controlled protocols that were performed in the mid-1980s suggested that zonisamide had efficacy for treatment of patients with refractory partial seizures.[2,3] However, drug development in the United States was halted when 3.7% of patients enrolled in studies developed renal calculi. Since studies in Europe and Japan showed both efficacy and safety[4,5] with lower rates of calculi formation, studies in the US were resumed in the 1990s.

As detailed in the following reports, bioavailability and bioequivalence were evaluated in five studies of 72 patients and healthy volunteers aged 19–69 years. Fourteen studies of 172 patients and healthy volunteers aged 18–71 years reported the effects of other drugs including AEDs, and both food and renal function on zonisamide pharmacokinetics. Data showed that plasma clearance of zonisamide is increased when administered along with other drugs that induce hepatic enzymes. Zonisamide kinetics are similar in young and elderly patients and are unaffected by food. Decline of renal function is associated with decreased zonisamide clearance. Plasma half-life of zonisamide measured in healthy volunteers given 400 mg/day was reported to be 63–69 h.[6] Because of drug interactions, the half-life of zonisamide is significantly decreased in patients treated with phenytoin, carbamazepine, phenobarbital, or valproate.[2]

As reviewed in detail by Dr. Faught in this document, clinical trials studied 810 patients aged 12—79 years. Many patients were treated for more than 1 year in follow-on open-label studies. Median seizure frequency was reduced from 13.9 to 50.1%. Responder rates, an expression of the percent of patients having a greater than 50% seizure reduction, ranged from 28.0 to 55%. Open-label assessment reported that a 52% reduction of seizures from baseline was associated with a dosage of 500 mg/day.[3] The responder rate in this study was 41%. A European study reported an association of a zonisamide plasma level of 30 μg/mL resulted in a decrease of 27% in seizures of partial onset.[4] A summary of data from 1008 patients treated in various protocols in Japan reported doses ranging from 5.9 to 8.2 mg/kg per day resulted in a responder rate of 50 to 60%.[5] A multicenter randomized, placebo-controlled study of patients with refractory partial-onset seizures reported first dose efficacy of 100 mg/day resulting in 20.5% reduction of

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seizures. A dose of 400 mg/day resulted in a 42% responder rate. Adverse events were infrequent and the drug was well tolerated.[7] Doses in adults of 400–600 mg/day corresponded to 7 mg/kg per day.

Adverse effects in studies showed that zonisamide causes weight loss and is associated with the occurrence of somnolence, anorexia, and ataxia. Renal calculi continued to be detected but the percentage of all studied patients was low.

In 1997, as data collection from the US clinical trials was completed, Dainippon entered into a licensing agreement with Elan Pharmaceuticals for marketing and distribution of zonisamide in North America and Europe. Zonisamide was approved for use in the United States in March 2000.

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